

VIEWPOINT

The Ethics of Continuing Placebo in SARS-CoV-2 Vaccine Trials

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As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to rage, developing safe and effective vaccines is critically important. With unprecedented speed, multiple candidate vaccines are now being evaluated in placebo-controlled clinical trials that have enrolled hundreds of thousands of participants.

According to Pfizer-BioNTech and Moderna, interim analyses after approximately 2 months of follow-up suggest their vaccines are 90% to 95% effective at preventing SARS-CoV-2 infection, although no peer review of the data has been conducted to date. Both companies now claim they have an “ethical obligation” to offer vaccine as soon as possible to all participants who received placebo, considering the strong results and participants’ contribution to the research.^{1,2}

This Viewpoint argues that given limited vaccine supply for at least several months, only the participants receiving placebo who would be eligible for vaccination outside the trial should be offered access to the vaccines at this point. The argument is explored in the US context, setting aside ethical questions about global vaccine distribution.

If the US Food and Drug Administration grants an Emergency Use Authorization for the vaccines, as appears likely at the time of writing, the supply of vaccines will initially be limited. Government officials

Clinical trials should offer vaccine to participants in the placebo groups who would be eligible for vaccination outside the trial.

project that at most 40 million doses will be available in December 2020.³ This amount would be sufficient to vaccinate 20 million people, a fraction of what would be needed to protect the population. Priorities for vaccination therefore need to be set.

Several ethical frameworks for prioritizing groups for vaccination have been developed, with significant overlap between frameworks (eAppendix in the Supplement). For example, the Advisory Committee on Immunization Practices to the Centers for Disease Control and Prevention has identified 4 priority groups with a view to maximizing benefits and minimizing harms, promoting justice, and mitigating health inequities: health care personnel, other essential workers, adults with high-risk medical conditions, and adults aged 65 years or older.⁴ Decisions about continuing coronavirus vaccine trials should be consistent with these ethical frameworks.

Under conditions of vaccine scarcity, 2 ethical reasons conflict with offering vaccine to all participants in the placebo group. First, this would result in a major loss of valuable research data without eliminating undue risks to participants who continue in the placebo group of the trials. Second, health and health equity gains would decrease because participants in the placebo group would be given vaccine even when they have not been prioritized for vaccination outside the trial.

Data about the long-term safety and efficacy of vaccines are essential to support their full licensure and their intended widespread, government-financed use. For example, important uncertainties remain about the duration of the high protective efficacy of the vaccines; whether measures of immune function, such as neutralizing antibody titers, predict any waning of immunity; whether enhanced disease occurs following vaccine waning; and the safety and effectiveness of vaccines in different demographic groups as well as long-term safety. The best way to resolve these uncertainties is to continue placebo-controlled trials, given the substantial risks of bias in observational studies of vaccine effectiveness,⁵ especially under rapidly changing circumstances.

Crucially, if all participants in the placebo groups of vaccine trials were offered vaccine, valuable research data would be lost even though continued placebo use would not necessarily expose participants to undue risks.

A key question for evaluating participants’ risks is whether they are eligible for vaccination outside the trial. Although policies will differ by state, they should be guided based on the various ethical frameworks that have been developed, such as the framework from the Advisory Committee on Immunization Practices.⁴ If participants are not eligible for vaccination outside the trial, continuing in the placebo group would not make them worse off than they should have been outside of participating in the trial.⁶ The risks of continuing their participation in the placebo group could therefore be justified, provided the trials yield valuable research data and participants are encouraged to minimize the risks of SARS-CoV-2 infection.⁷ In contrast, if participants are eligible for vaccination outside the trial, continuing in the placebo group would make them significantly worse off than they should have been outside of participating in the trial. The risks to these participants seem difficult to justify; in any case, they could simply withdraw from the study and seek vaccination outside the trial.

Careful statistical adjustments would have to be made for removing participants in the placebo group, perhaps with an “intent-to-continue” analysis of only

those who are not eligible for vaccination outside the trial. There currently is limited information on how many participants in the ongoing trials would be offered vaccine because they belong to the identified top priority groups for vaccination. The proportion could be less than 10% if health care personnel (estimated at 21 million, 6% of the population)⁴ are prioritized exclusively in the first months of vaccine availability. The proportion could be greater if other priority groups are also eligible for immediate vaccine access. However, even with a reduced trial cohort, important data could be gathered, especially if SARS-CoV-2 infection rates remain high and several months of additional follow-up are possible.

The second ethical reason against offering vaccine to all participants in the placebo groups of the trials is that this would yield lower health and health equity gains from vaccination overall if participants do not belong to the identified priority groups. With a projected vaccine supply for at most 20 million people through the end of 2020,³ there will initially be barely enough vaccine to vaccinate even the top priority group identified across all ethical frameworks: the estimated 21 million health care personnel.⁴ Thus, if all participants in the placebo groups in the Pfizer-BioNTech trial (currently n = 43 651; placebo group, n = 21 828) and Moderna trial (n = 30 000; placebo group, n = 15 000) were offered vaccine, this would mean that currently up to 36 828 health care personnel or other individuals who have higher priority than the participants could not be vaccinated. The resulting loss of benefits could be significant.

Participants who received placebo in the vaccine trials have made an essential contribution to testing vaccine safety and efficacy. Notably, they made this contribution without any promise during the consent process that they would later be prioritized for vaccination.⁸ Participants in the placebo groups who are not eligible for vaccination outside the trial should not be placed ahead of groups that have been prioritized across ethical frameworks.

Above all, this would fail to maximize benefits and minimize harms because participants in the placebo groups who are not health care personnel do not have an instrumental role in the pandemic response, and participants younger than 65 years or without high-risk medical conditions benefit less from being vaccinated. Nevertheless, participants' research contributions could be partially recognized by offering the first vaccine doses to the participants in the placebo groups who belong to the identified priority groups for vaccination.

Based on these ethical and scientific considerations, the following practical steps are recommended. Sponsors and investigators should inform participants about the encouraging interim results, including whether an Emergency Use Authorization for the vaccines has been granted. They should then offer vaccine to participants in the placebo groups of clinical trials who would be eligible for vaccination outside the trial. Crossover to the vaccines should happen as part of the trial, so that follow-up data on immune responses and potential breakthrough infections can still be gathered. All other participants should remain blinded to whether they received vaccine or placebo in the trial and should be informed that while vaccine supplies are limited, vaccine is being offered only to the participants in the placebo group who would be eligible for vaccination outside the trial. These participants should be encouraged to remain enrolled in the trial to generate valuable research data while engaging in physical distancing, mask wearing, and other strategies to minimize the risk of SARS-CoV-2 infection. These participants should also be reminded that they have the right to withdraw from the trial without penalty. Finally, these recommendations should be revisited frequently with respect to the importance of continuing placebo-controlled trials and the degree of vaccine scarcity, especially as more vaccine doses and potentially other vaccines become available.

ARTICLE INFORMATION

Published Online: December 14, 2020.
doi:10.1001/jama.2020.25053

Conflict of Interest Disclosures: Dr Lipsitch reported receipt of honoraria/consulting fees from Merck, Affinivax, Sanofi Pasteur, Bristol Myers Squibb, and Antigen Discovery; receipt of research funding (institutional) from Pfizer; and provision of unpaid scientific advice to Janssen, AstraZeneca, One Day Sooner, and COVAXX (United Biomedical). No other disclosures were reported.

Funding/Support: This work was supported in part by the Clinical Center Department of Bioethics, which is in the Intramural Program of the National Institutes of Health.

Role of the Funder/Sponsor: The funder had no role in the preparation, review, or approval of the manuscript or decision to submit the manuscript for publication.

Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect the policies of the National Institutes of Health or the US Department of Health and Human Services.

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